Biology of Cancer

Introduction

In order to be a successful cancer, many things have to go wrong. It's not that one thing breaks and suddenly there's malignancy. One critical mutation can tip the scales, initiating a cascade of events that eventually leads to malignant transformation, but it is a series of events that culminates in malignancy, not one flip of a switch. Given the number of cell divisions that happen in any one human over a lifetime, the rate of malignant transformation (per cell division) is actually incredibly low. However, relative to the population of humans, cancer has a high incidence, prevalence, cost, and mortality. It only takes one cell to undergo malignant transformation amongst the billion in a human's lifetime to generate cancer. The chances are extremely unlikely that any one cell will transform. And even if a cell gets several mutations on its way to full malignancy, lots can go wrong for that naughty cell before it transforms, such as intrinsic mechanisms to silence a cell (senescence, intrinsic apoptosis), acquisition of catastrophic DNA damage (telomere crisis), being found by the immune system (extrinsic apoptosis), or simply running out of resources (necrosis). But all it takes is one cell to slip through the cracks. And if that one cell manages to accumulate enough mutations it is transformed. And once that transformation happens, because it has acquired sufficient mutations, that cell is incredibly difficult to get rid of because it already evaded all the safety mechanisms in transforming. From there, things just get worse. More and more mutations are tolerated and the cancer progresses.

The most important thing to start with in this lesson is that malignant transformation is caused by an accumulation of mutations which result in both **gain of function of oncogenes** and **loss of function of tumor suppressors**. When the cell has accumulated sufficient traits, through a sufficient number of mutations, the cancer finally becomes malignant.

This lesson is going to be about both the themes of malignant transformation—self-sufficiency, escapes immunity, escapes apoptosis, unregulated growth, immortalization, angiogenesis, and invasion—as well as some of the high yield examples that illustrate these overarching concepts. The successful traits of cancer are provided in table 7.1 and are the subject of the discussion that follows. As we progress into the organ system modules beyond The Cell, we will study specific malignancies. As we study specific malignancies, we will introduce new genes, new mutations as part of the pathogenesis of that malignancy being discussed. The examples in this lesson are not meant to be an exhaustive list. For each trait we have chosen an example from what you have already studied in this course so far to keep the discussion familiar.

The traits of a successful cancer are:

NORMAL CELLS			MALIGNANT TRAIT
1 Grow when told to	Growth Factor	GAIN of function = Oncogene	1 Self-Sufficient Autocrine
2 Die when told to	Death-Receptor Fas-FasL Caspaces	LOSS = Tumor Supressor	2 Escapes Immunity
3 Die when damaged OR Repair the damage	p53, ATM, Rb MDM2	LOSS = Tumor Supressor GAIN = Oncogene	3 Escapes Apoptosis Tolerates Genomic Instability
4 Cooperate with others	E-cadherin β-catenin	LOSS = Tumor Supressor GAIN = Oncogene	4 Ignores Boundaries, Limitless growth
5 Limited Proliferation	Crisis/Death	Gain Telomerase	5 Immortilization
6 Cannot grow vessels	VEGF MMP	Gain = Oncogene	6 Angiogenesis
7 Stays Put	VEGF MMP	Gain = Oncogene	7 Invasion/Metastasis

DE DIFFERENTIATION

Table 7.1: The Traits of Malignancy
The first four allow for proliferation. Sustained angiogenesis allows for a tumor, benign or malignant, to sustain that proliferation. Toleration of genomic instability and immortalization are necessary mutations for malignancy to develop. Tissue invasion defines malignancy. Over time, de-differentiation occurs.

Successful Traits of Cancer (in no order)

Self-sufficiency. If a normal cell fails to receive trophic signals, the default is to undergo apoptosis. A cancer cell **gains** the ability to **sustain itself**. It can be by developing **autocrine** trophic factors or, if later in the transformation steps, a **paracrine** signal from its own daughters, where the mass of cancer cells keep each other alive.

Escapes immunity. The immune system is constantly looking for abnormal behavior from cells. Whether a cancer transformation or a cell infected by a pathogen, the host immune system can induce apoptosis in an affected cell. This is done with death receptors such as the Fas-FasL, perforins/granzymes, or TNF-α. A cancer cell loses the ability to receive death signals. This event often occurs in the form of a **loss-of-function** mutation, silencing the expression of the death receptor.

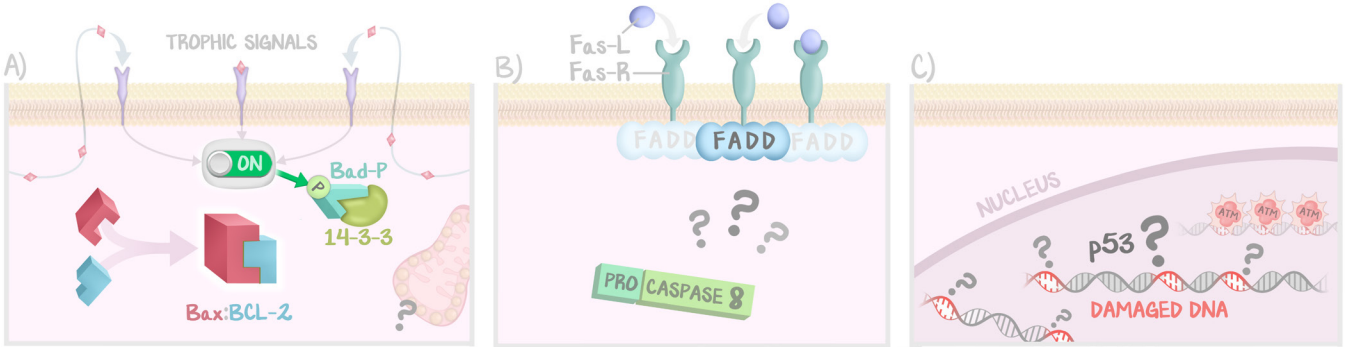

Figure 7.1: Evading Apoptosis
(a) Gain of function, self-sufficient production of autocrine signaling, or intratumor paracrine signaling prevents apoptosis. (b) Loss of function of extrinsic apoptotic signals prevents immune cytokines from inducing apoptosis. (c) Loss of function of tumor suppressors tolerates damaged DNA and escapes apoptosis.

Evades apoptosis, ignores damaged DNA. Not only does a cancer cell lose the ability to listen to a death signal (silenced extrinsic anti-proliferation), a cancer cell also loses its safety measures. Tumor-suppressor genes exist to check for errors, and to arrest the cell cycle or induce apoptosis if they are found. A **loss of tumor-suppressor genes** would mean that errors could not be identified or fixed. The checkpoints come down, or the signals that normally induce a cell into apoptosis (such as proliferation of DNA errors) are no longer made. This is often in the way of a **loss of function** of tumor suppressors. The famous ones are the **loss of p53** and the **loss of Rb**.

Unregulated growth. In wound healing, cells proliferate and migrate towards each other until they bump into each other. If they didn't, our wounds would never heal. Cells know when they bump into each other through extracellular protein interactions such as E-cadherins. The extracellular E-Cadherin of one cell touches the extracellular E-Cadherin of another and the intracellular signal to proliferate that was disinhibited by the missing neighbor becomes inhibited again by the presence of a neighbor. Cancer cells continue to proliferate, undeterred by these normal mechanisms that should keep them from overgrowing. Besides loss of cell-to-cell signaling molecules themselves (**E-cadherin**), proliferation dysregulation could be due to alteration of intracellular mechanisms that modulate proliferation. One such intracellular mechanism involves β-catenin. E-cadherin inhibits β-catenin's release. APC normally degrades β-catenin. Receptor Tyrosine Kinases can stimulate β-catenin. β-catenin is a transcriptional growth factor. If its activity increases, the cell proliferates. Any one mutation that tips in favor of β-catenin results in increased proliferation, be it a **loss of function** of E-Cadherin or APC, or a **gain of mutation** of an overactive RTK.

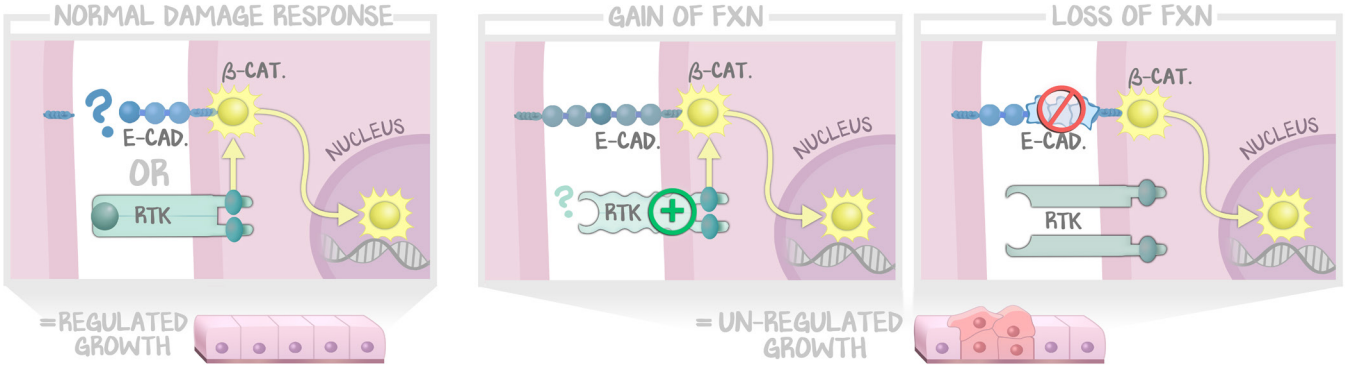

Figure 7.2: Unregulated Growth
Either by loss of cell to cell recognition signal of E-cadherin releasing β-cadherin or by the activation of a receptor tyrosine kinase stimulating release of β-catenin, β-catenin will promote proliferation. That means either a gain -of-function mutation in the RTK or a loss-of-function in the E-cadherin could result in increased cell proliferation.

Immortalization. All cells need DNA to live, even cancerous ones. All cells have a set number of divisions before they die, determined by telomeres. **Telomeres shorten** with each cell division. If the cells were to just keep dividing, they would eventually run out of telomeres, and that would expose chromosomes. Exposed chromosome ends are interpreted as double-stranded breaks. These breaks are repaired by attaching chromosomes one to another. This results in catastrophic anaphase arrangements. This is a cell in **telomere crisis.** Unregulated proliferation would solve itself with telomere crisis. This may be why we see so few malignant transformations, despite the billions of cellular divisions in our body (most malignant transformations die in telomere crisis, so we don't ever detect them). But a cell that could restore its telomeres, a cell that **gains the function of telomerase**, is said to have undergone **transformation** and is now **immortal.** The activity of telomerase restores the cell from telomere crisis. Once transformed, the process is indefinite and the cell can continue to divide forever without fear of DNA death.

Up to this point, these mutations have resulted in unregulated proliferation. The cell will divide and overgrow its neighboring good cells. These features allow a tumor to grow. A tumor is not a malignancy. Neoplasia is just unregulated growth. For a tumor to become malignant, it needs a few other things.

Angiogenesis

All cells need oxygen and glucose to live. A cancerous cell starts in the organ it which it grows, and it has a blood supply. As that cell begins to proliferate without regulation, more and more cells means more and more metabolic demand. Those tumors that grow too quickly will outgrow their blood supply and become necrotic. But smart cancer cells are able to **produce new blood vessels from existing ones**, a process called **angiogenesis**. Recall from Lesson #4 that angiogenesis is required for wound healing. The highly metabolic fibroblasts require a temporary dense network of capillaries at the wound site. The creation of that temporary dense network of capillaries is the same angiogenesis that cancers perform. Through various endothelial growth factors such as Vascular Endothelial Growth Factor **(VEGF)**, Platelet-Derived Growth Factor **(PDGF)**, and **TNF-β**, normal healthy blood vessel endothelium shifts from a **quiescent** to a **proliferative** state, growing more endothelial cells. At the same time, fibroblasts secrete matrix metalloproteinases **(MMPs)** to alter the architecture of the surrounding tissue to let those vessels in.

Cancer cells hijack the normal process of healthy wound healing in order to supply a growing tumor with its own blood supply.

Malignancy, Tissue Invasion, Metastasis

Becoming malignant means that there must be (1) a loss of cell adhesion molecules, and (2) activation of extracellular MMPs. Now we see some overlapping effect. Gain of MMPs was needed for angiogenesis. Loss of adhesion molecules allowed for unrestricted growth. Now here, similar features allow for tissue invasion and metastasis.

Invasion describes the tumor's ability to penetrate the capsule or basement membrane. Metalloproteinases (MMPs) of various kinds are used to disrupt extracellular matrix proteins to allow blood vessels in. These same MMPs (don't learn the different names, keep it general) can degrade the basal lamina and allow migration or proliferation into the extracellular matrix. Further invasion, proliferation, and migration allows individual malignant cells to reach for the lymphatics and blood vessels.

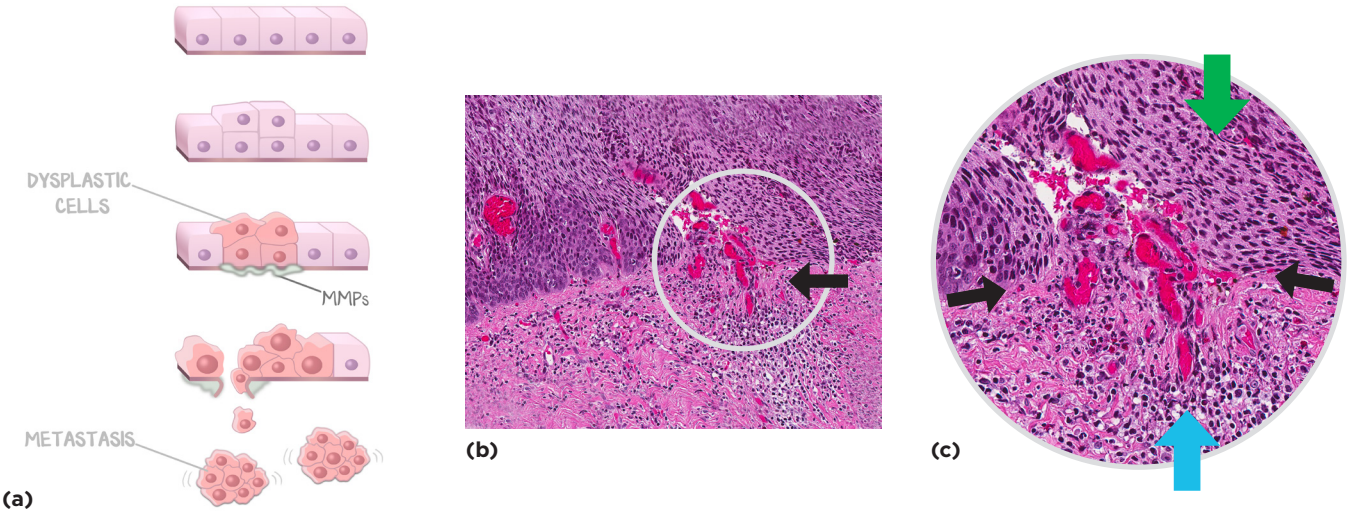

Figure 7.3: Malignant Traits
(a) Progression of unregulated proliferation alone (benign tumor) into an invasive malignancy. The same metalloproteinases that permitted angiogenesis and wound healing now allow malignant cells to penetrate the basement membrane. Growth of malignant cells in sites distant from the origin is called metastasis. (b) Light microscopy showing invasion of the basement membrane of an epithelial layer at low power (c) high power view showing the broken basement membrane (black arrows), hemorrhage, at the dysplastic epithelial layer (green arrow) and the inflammatory reaction of leukocytes (blue arrow).

Metastasis is the growth of a cancerous colony distant from the origination site and noncontiguous with the original cancer. Having penetrated the basement membrane (invasion), the cancerous cells can then **disseminate**. When a cancer cell reaches systemic circulation (either through embolism from hematogenous spread or by making it through the lymphatics), it can **circulate freely** to all organs.

Implantation occurs when the malignant cell invades a new tissue distal to the original source, and begins proliferation there as well.

Metastatic patterns are discussed in #10 *General Concepts of Neoplasia*.

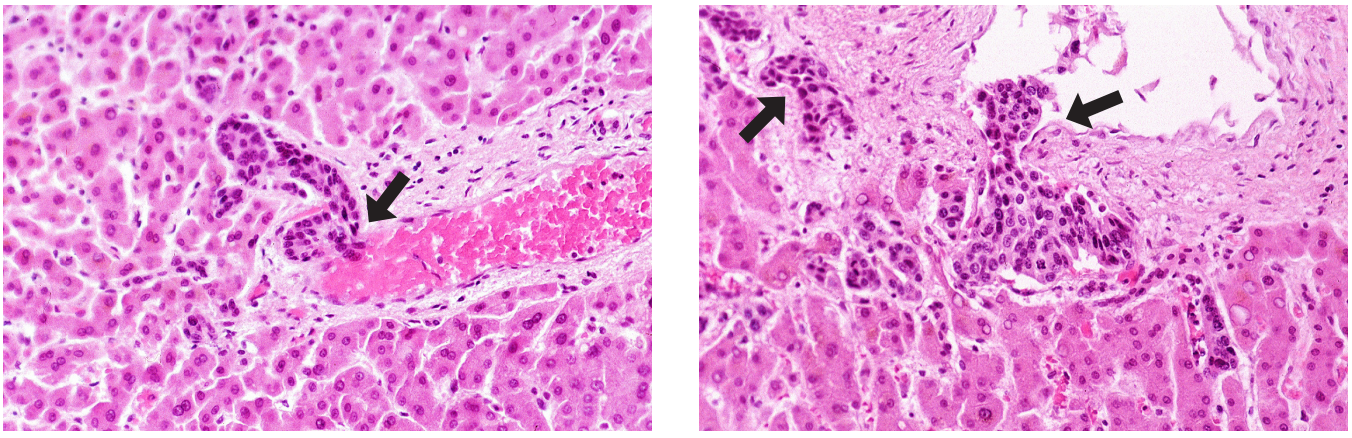

Figure 7.4 Metastasis
(a) Breast cancer metastasis in liver. This clump of metastatic cells is transiting through the wall of the blood vessel (arrow). (b) Breast cancer metastases inside lymphatics of liver (arrows).

270+: The Details of the Stem-Cell Theory of Cancer

The theory is that it only takes one cell to breed cancer. One cell develops sufficient mutations to become malignant. That one cell is the stem cell. It then makes all the cancer cells, some clones of the stem cell (making another stem cell), and some just regular cancer cells.

Stem cells operate differently than other cancer cells. Stem cells, when they divide, make a copy of themselves as a progenitor. Careful with the words. It's the same physical process as mitosis—one cell becomes two clones. But with **asymmetric mitosis** the stem cell stays the same and spawns a single clone. The **progenitor cell** that's made from that stem cell loses its stem-cell powers and becomes like every other cell. When the progenitor cell divides, it's **symmetric**—as we've discussed, one cell becomes two daughters.

Stem cells are totipotent. Progenitor cells are omnipotent. Differentiated cells are fixed. Cancer takes a step back. So cancer can be seen as two populations of malignant cells. A **large** population of **rapidly dividing progenitor cells** and a very **small** population of **slowly dividing stem cells**. This has implications for treating cancer (chemotherapy targets the bulky rapidly dividing cells and cannot accurately target the stem cells), but more importantly it has implications for **how malignancy begins**. Just one cell—just one—has to undergo malignant transformation.

That malignant stem cell comes from normal healthy cells. A normal healthy human cell DOES NOT "flip" from normal healthy to fully malignant, but a normal healthy human cell DOES "flip" into the cascade that will lead to malignancy. It isn't "normal cell" to "invasive metastasis" that starts the cascade, but rather "cooperating cell" to "small survival benefit mutation." That flip is called the **initiating event**. Without an initiating event, cancer cannot exist. That one mutation, for whatever reason, allows for either genomic instability or massive proliferation. This is basically the event that allows a cell to gain a growth or mutagenic advantage (either it grows, or incorporates mutations, or both). There is no "one event." Any number of a thousand events can occur. But when one does, if that cell line proliferates more than the others, it has more opportunity to flip more switches towards malignancy.

A **growth advantage** could be any of the traits that promote proliferation. The cell tells itself to grow (autocrine), escapes the ability to be turned off (death receptors), or silence itself (apoptosis). So it proliferates. And with an **increased proliferation** simply comes more opportunity for more errors. Benign tumors are not malignant, but their increased proliferation rates expose them to the peril of additional mutations, and thereby generating malignant clones."

Genomic instability refers to a mutation that results in the inability to identify or repair DNA. While the growth advantage may allow proliferation despite the error (escaping apoptosis), genomic instability is the real danger to malignant transformation. Genomic instability has a steamroller effect. As more proliferations occur, more mutations are tolerated, and more genes break. More oncogenes are activated and more tumor suppressors are silenced. Some mutations kill the cell. But the cells that live are the ones that proliferate. And with each proliferation the mutations get worse. This is how a cell can **de-differentiate**, becoming less and less the cell it started as by expressing an unregulated set of genes.

That one stem cell with the initial growth advantage or genomic instability proliferates, albeit slowly, and accumulates more and more mutations. Eventually the right combination of traits is reached, and it becomes fully malignant.

The goal is to identify the initiating event and either prevent it or use molecular therapies that target the **stem cells directly** rather than going after the progenitors.